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A Long-Term Follow-up Report on Allogeneic Stem Cell Transplantation for Patients with Primary Refractory Acute Myelogenous Leukemia: Impact of Cytogenetic Characteristics on Transplantation Outcome

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ABSTRACT

The prognosis of patients with primary refractory acute myelogenous leukemia (AML) is poor. Our initial report suggested that some patients could achieve durable remission after allogeneic stem cell transplantation (SCT). Herein, we update our initial experience and report further analysis of this group of patients to determine whether there are pre-SCT prognostic factors predictive of posttransplantation relapse and survival. We reviewed the records of 68 patients who consecutively underwent transplantation at the City of Hope Cancer Center with allogeneic SCT for primary refractory AML between July 1978 and August 2000. Potential factors associated with overall survival and disease-free survival were examined. With a median follow-up of 3 years, the 3-year cumulative probabilities of disease-free survival (DFS), overall survival (OS), and relapse rate for all 68 patients were 31% (95% confidence interval [CI], 20%-42%), 30% (95% CI, 18%-41%), and 51% (95% CI, 38%-65%), respectively. In multivariate analysis, the only variables associated with shortened OS and DFS included the use of an unrelated donor as the stem cell source (relative risk, 2.23 [OS] and 2.05 [DFS]; P = .0005 and .0014, respectively) and unfavorable cytogenetics before SCT (relative risk: 1.68 [OS] and 1.58 [DFS]; P = .0107 and .0038, respectively). Allogeneic SCT can cure approximately one third of patients with primary refractory AML. Cytogenetic characteristics before SCT correlate with transplantation outcome and posttransplantation relapse.

KEY WORDS

Acute myelogenous leukemia • Allogeneic stem cell transplantation • Cytogenetic characteristics • Treatment failure

INTRODUCTION

The survival of patients with acute myelogenous leukemia (AML) who do not achieve a remission with primary induction therapy is poor. After induction with conventional chemotherapy regimens, such as the combination of 3 days of anthracycline and 7 days of conventional-dose cytarabine (100-200 mg/m^2/d), approximately 30% of patients will not achieve a remission [1]. Of this group, selected patients may still respond to a high-dose cytarabine-based (2-3 g/m^2) salvage regimen, but cure is rare [2]. Our initial report included 14 patients with primary refractory AML and strongly suggested that some patients can achieve durable remission after allogeneic stem cell transplantation (SCT) [3]. Data from the International Bone

Marrow Transplant Registry (n = 88) [4] and the Société Française de Greffe de Moelle (n = 69) [5] reported a 3-year disease-free survival (DFS) of 21% and 9%, respectively, for similar patients. On the basis of these reports, allogeneic SCT has become a treatment option for patients with primary refractory AML, but few series have analyzed the prognostic factors that determine transplantation outcome. In this study, we updated our initial experience to include 68 patients with primary refractory AML who underwent transplantation in the City of Hope BMT program. We analyzed this group of patients to determine whether there are pre-SCT features that predict treatment failure after transplantation.

PATIENTS AND METHODS

We reviewed the records of 68 patients who consecutively underwent transplantation at the City of Hope Comprehensive Cancer Center with allogeneic SCT for primary refractory AML from July 1978 to August 2000. This study was approved by the institutional review board according to institutional standard practice. Patients were eligible for this study if they had never achieved a first complete remission with chemotherapy. Complete remission was defined as <5% blasts in the bone marrow and normalization of the peripheral blood count without circulating blasts. Patients were not eligible for allogeneic SCT if they had severe concomitant medical or psychiatric illnesses, had active central nervous system leukemia, or were seropositive for human immunodeficiency virus or human T-cell lymphoma virus-1. Other exclusion criteria included a bilirubin level >2 mg/dL, a creatinine clearance <80 mL/min, a cardiac ejection fraction of <50%, and a forced expiratory volume in 1 second and/or diffusing lung capacity <50% of the predicted value.

Cytogenetic risk group analysis was performed according to Southwest Oncology Group guidelines [6]. Three cytogenetic categories were defined. The favorable-risk category included patients with abnormalities of inv(16)/t(16;16) or t(15;17) with any additional abnormalities or t(8;21) without either having a del(9q) or being part of a complex karyotype. The intermediate-risk category included patients characterized by +8, −Y, +6, del(12p), or a normal karyotype. The unfavorable-risk category was defined by the presence of 1 or more of −5/del(5q); −7/del(7q); inv(3q); abnormal 11q, 20q, or 21q; del(9q); t(6;9); t(9;22); abnormal 17p; and a complex karyotype, defined as ≥3 abnormalities.

Factors associated with overall survival (OS) and DFS were examined by univariate Cox regression analysis. The risk ratio was calculated for each variable tested, along with the 95% confidence interval (CI). Stepwise Cox regression was performed to determine independent predictors of relapse and survival; all variables with $P < .10$ on univariate analysis were included as candidates in the analysis. Survival estimates were calculated on the basis of the product-limit method of Kaplan and Meier, and comparisons between subgroups were made with the log-rank test. The 95% CIs were calculated by using the logit transformation and the Greenwood variance estimate. The Wilcoxon ranked sum test was used in comparing medians for continuous data, and the Pearson χ^2 test was used to compare the incidence of graft-versus-host disease (GVHD) between treatment regimens. The following variables were examined for their effect on outcome: age at transplantation, sex, white blood cell count (WBC) at diagnosis, number of cycles of induction chemotherapy, treatment with high-dose cytarabine-based regimens, WBCs before transplantation, cytogenetic risk group, percentage of blasts in blood or bone marrow at the time of the transplantation, conditioning regimen (total body irradiation [TBI] based versus chemotherapy based), and interval between diagnosis and transplantation.

RESULTS

Patient Characteristics and Outcome

The demographic data and disease characteristics are shown in Table 1. The median age at SCT was 37 years (range, 2-62 years). Sixty percent of patients experienced treatment failure with at least 1 cycle of a high-dose cytarabine-based regimen, and 60% received at least 2 prior regimens before SCT. The median interval from diagnosis to SCT was 3.3 months (range, 0.8-10.3 months). The median percentage of blasts in the bone marrow was 36% (range, 1% to >90%). Fifty (74%) patients had evaluable pretransplantation cytogenetics categorized as follows: 2 had favorable, 27 intermediate, and 21 unfavorable cytogenetics. Fifty-two patients (76%) received a TBI-based conditioning regimen. Fifty-six patients (82%) received stem cells from matched related donors and 12 (18%) from matched unrelated donors. All patients received unmodified bone marrow or granulocyte colony-stimulating factor–primed peripheral blood stem cells. During the study period, patients were also enrolled in ongoing GVHD prophylaxis studies [7,8]. GVHD prophylaxis consisted of cyclosporine and prednisone in 28%; cyclosporine and methotrexate in 19%; cyclosporine, prednisone, and methotrexate in 26%; and others in 26%.

For patients who survived to the date of analysis, follow-up ranged from 1 to 18 years, with a median of 3 years. At the time of this analysis, 18 patients were alive and in continuous remission. Twenty-eight patients had a relapse (median time to relapse, 9.3

Table 1. *Patient Characteristics and Transplantation Procedures*

Variable	n (%)
Patient Characteristics	
Age	
≤30 y at transplant	17 (25)
>30 y at transplant	51 (75)
Sex	
Male	34 (50)
Female	34 (50)
Prior treatment with High-dose cytarabine-based regimen	
Yes	41 (60)
No	27 (40)
No. of prior regimens	
≤2	56 (82)
>2	12 (18)
Transplantation characteristics	
Related Donor	
Genotypic-identical	54 (79)
Phenotypic-identical	2 (3)
Unrelated donor	
HLA-identical	7 (10)
HLA mismatched	5 (7)
Conditioning regimen	
FTBI + cyclophosphamide + others	17 (25)
FTBI + busulfan + VP-16	16 (24)
FTBI + busulfan	12 (17)
Busulfan + cyclophosphamide	6 (9)
Others	4 (6)
GVHD prophylaxis	
CSA alone	1 (1)
CSA + Pred	19 (28)
CSA + MTX	13 (19)
CSA + Pred + MTX	18 (26)
Others	17 (26)

CSA indicates cyclosporine; Pred, prednisone; MTX, methotrexate; FTBI, fractionated total body irradiation.

months; range, 0.9-43.5 months), and 22 died of nonrelapse causes. Most of the relapses (27/28; 96%) occurred within the first year after SCT.

The 3-year cumulative probabilities of DFS, OS, and relapse rate (RR) for all 68 patients were 31% (95% CI, 20%-42%), 30% (95% CI, 18%-41%), and

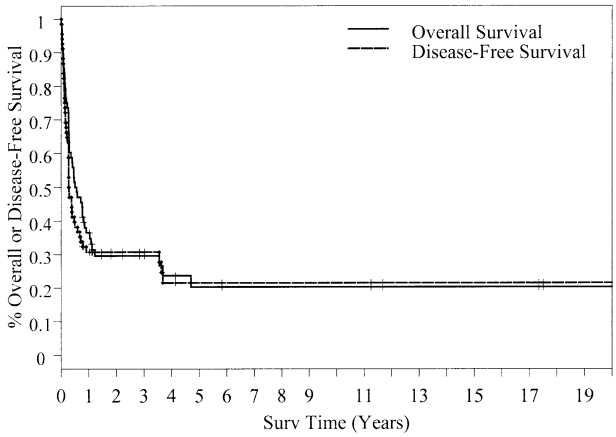

Figure 1. Overall and disease-free survival (n = 68).

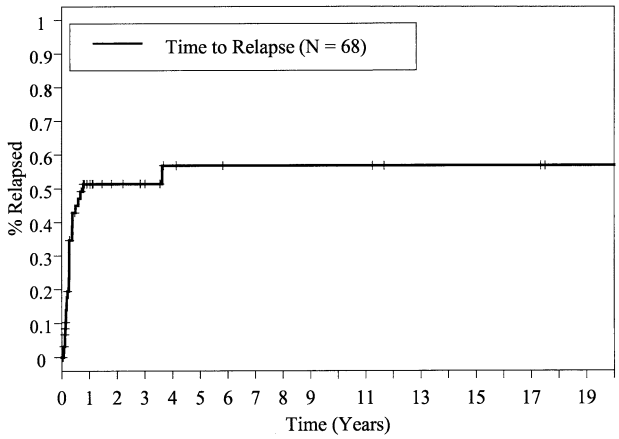

Figure 2. Time to relapse for all 68 patients with primary refractory AML.

51% (95% CI, 38%-65%; Figures 1 and 2). The 3-year probabilities of DFS and RR at 3 years were 44% (95% CI, 25%-63%) and 37% (95% CI, 17%-58%), respectively, for patients with intermediate cytogenetics and 18% (95% CI, 1%-35%) and 57% (95% CI, 31%-83%), respectively, for patients with unfavorable cytogenetics (Figures 3 and 4). The differences in DFS and OS between the 2 groups were significant by log-rank test ($P = .0071$ and $P = .0147$, respectively). The difference in probability of relapse was also significant ($P = .0264$ by the Wilcoxon test). The DFS for related donors (n = 56) and unrelated donors (n = 12) was 36% and 8%, respectively (log rank; $P = .0005$; Figure 5).

Prognostic Factors

Univariate and multivariate stepwise Cox proportional hazard analyses of patient characteristics were performed to determine risk factors for OS and DFS. In the multivariate stepwise model, the only variables associated with shortened OS and DFS included the use of an unrelated donor as the stem cell source

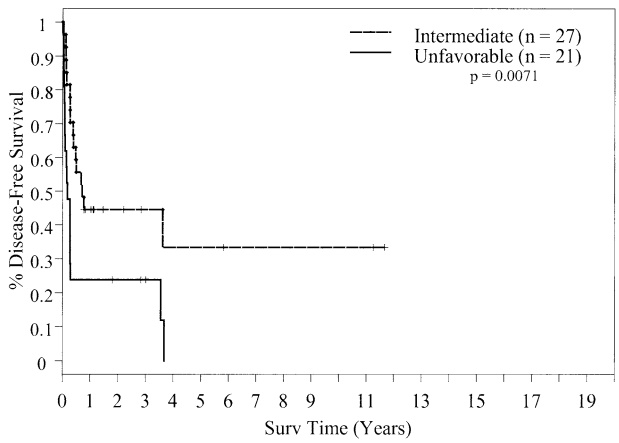

Figure 3. Kaplan-Meier disease-free survival for patients with intermediate and unfavorable cytogenetics.

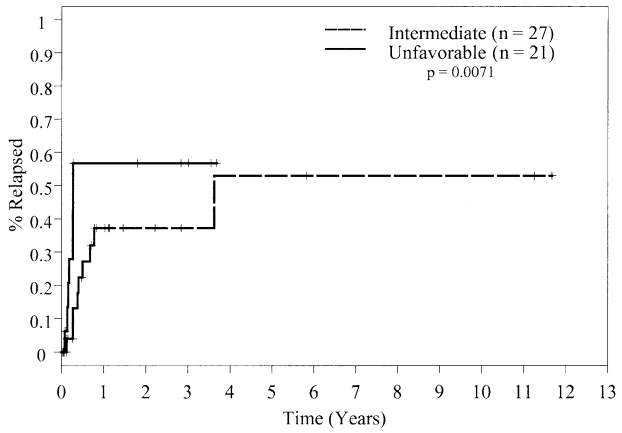

Figure 4. Kaplan-Meier time to relapse for patients with intermediate and unfavorable cytogenetics.

(relative risk, 2.23 [OS] and 2.05 [DFS]; $P = .0005$ and .0014, respectively) and unfavorable cytogenetics before SCT (relative risk, 1.68 [OS] and 1.58 [DFS]; $P = .0107$ and .0038, respectively). Age at transplantation, sex, WBCs at diagnosis, number of cycles of induction chemotherapy, prior treatment with high-dose cytarabine-based regimens, pretransplantation WBCs, percentage of blasts in the blood or bone marrow before SCT, conditioning regimens (TBI based versus chemotherapy based), and the interval between diagnosis and SCT did not affect DFS or RR.

The 38 patients who survived in remission to day 100 were analyzed to assess whether chronic GVHD had any influence on RRs. For the 29 patients without chronic GVHD, the probability of relapse at 3 years was 41%, whereas the probability of relapse at 3 years for the 9 patients who did develop chronic GVHD was 35%. The difference was not significant by log-rank test ($P = .55$).

DISCUSSION

Most patients with primary refractory AML die from either disease progression or chemotherapy-related complications within months from diagnosis. This long-term follow-up report indicates that approximately 30% of patients with primary refractory disease can still be cured with allogeneic SCT. In our series, the 3-year DFS for patients with intermediate-risk cytogenetics was 44%, and the outcome was similar to that of patients who underwent transplantation at first relapse or second complete remission, despite the refractory nature of the disease [9,10]. Nevertheless, the actual proportion of patients who can be cured with this approach remains unclear, because some patients will be excluded from a transplant option because of poor performance status, active infection, or inadequate organ function after 1 or more induction therapies. In addition, many patients cannot find a suitable HLA-matched donor in a timely fashion. This underscores the importance of including HLA typing as part of the initial assessment for all patients with AML and also for their potential donors.

Prior studies of allogeneic SCT in patients with refractory leukemia were associated with high treatment-related toxicity and mortality. In a report from the International Bone Marrow Transplant Registry [4], the 3-year treatment-related mortality (TRM) was 44%, and Mehta et al. [11] reported a TRM of 70% in their series of 24 patients. In our series, despite the inclusion of 13 patients (18%) who underwent matched unrelated donor SCT, the overall TRM in the entire cohort was similar to that of patients who received an allogeneic SCT at first remission [12]. The high TRM in the International Bone Marrow Transplant Registry study may be due to patient selection, because 25% of patients had clinically significant infections at the time of transplantation, and 60% of patients had Karnofsky performance scores $<90\%$.

Our initial report and other published single-center transplant series were too small to allow identification of prognostic factors to predict transplantation outcome in patients with primary refractory AML. The largest reported series for this unique group of patients was from the International Bone Marrow Transplant Registry [4]. In this study, by univariate analysis, $<25\%$ blasts in the bone marrow before transplantation, fewer than 4 prior induction regimens, and a Karnofsky performance score ≥ 90 were associated with an improved leukemia-free survival. In the same report, the presence of circulating blasts at bone marrow transplantation, female sex, and $>25\%$ blasts in the bone marrow were associated with an increased risk for relapse. In contrast, none of these factors was found to be associated with transplantation outcomes in our analysis. The reasons for the differ-

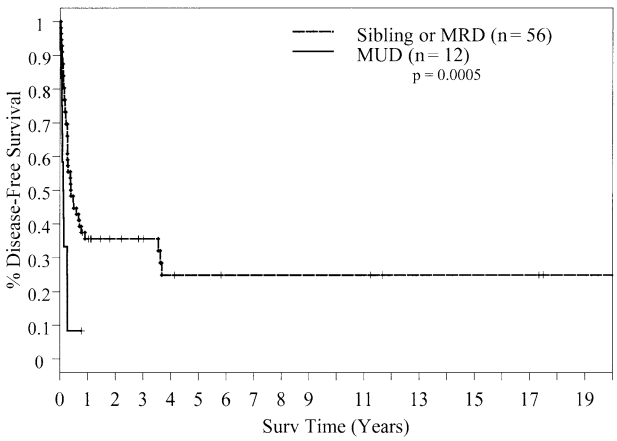

Figure 5. Disease-free survival for patients with related donors versus unrelated donors. MRD indicates matched related donor; MUD, matched unrelated donor.

ences are unclear, but our study suggests that allogeneic SCT can overcome the chemoresistance even in patients with frank leukemia at transplantation (ie, >25% blasts in the bone marrow).

A recent report from the US intergroup [6] has shown that cytogenetic characteristics present at diagnosis are associated not only with responses to induction therapy in adults with AML, but also with outcomes of postremission therapy. Cytogenetics are also the strongest predictive factor for outcomes in patients with AML who underwent transplantation in first complete remission [13]. Cytogenetic analysis data, however, were not available in other published reports for primary acute refractory myelogenous leukemia [4,5,11]. As shown in Figures 3 and 4, this analysis indicates that cytogenetic characteristics before SCT correlate with transplantation outcome and posttransplantation relapse. The presence of unfavorable cytogenetics before SCT predicted an adverse outcome. Our results compare favorably to those of other reported series [4,5,11], in which 3-year DFS ranged from 9% to 21%. The differences in the transplantation outcomes may be due to a difference in the distribution of the cytogenetic risk groups.

The transplantation outcomes for patients who received an unrelated SCT in this study are poor, with a 2-year DFS of only 8%. The results, however, are in accordance with other previously published reports. In an analysis of 70 patients with AML, the DFS for patients who underwent transplantation in first or second remission from an unrelated donor was 45%, and for patients with more advanced disease, DFS was 19% [14]. Sierra et al. [15] from the Fred Hutchinson Cancer Research Center performed transplantations in 16 patients with primary induction failure from an unrelated donor, with 5-year leukemia-free survival and RRs of 19% and 63%, respectively. The reasons for the poor outcomes are multifactorial but may include suboptimal HLA matching, prolonged neutropenia before SCT, and repeated salvage attempts with consequent organ toxicity while a suitable donor was sought. In our series, the interval between diagnosis and allogeneic SCT was 3.0 and 4.8 months for the related donor group and unrelated donor group, respectively ($P = .22$). In addition, 5 (42%) of 12 unrelated transplant recipients received a transplant from a ≥1 locus–mismatched donor, which has been shown to adversely affect the transplantation outcomes [16].

Disease progression after transplantation remains the major cause of treatment failure, in particular for patients who belong to the unfavorable cytogenetic risk group. The 3-year probabilities of DFS and relapse were 18% and 57%, respectively, for patients with unfavorable cytogenetics. The high RRs after SCT suggest that current high-dose chemoradiation regimens are often inadequate to eradicate leukemia. Multiple preparative regimens have been tested in the phase II setting in an attempt to improve the outcomes in patients with advanced leukemia, but none of them has demonstrated any superiority over other regimens. In a phase III randomized study, the Southwest Oncology Group compared fractionated total body irradiation and etoposide (FTBI/VP-16) with busulfan and cyclophosphamide. With a median follow-up of 52 months, the 2-year DFS was 17% and 24% for the TBI/VP-16 arm and the busulfan/cyclophosphamide arm, respectively ($P = .81$). Newer specific antimyeloid conditioning regimens are being tested. Investigators from the City of Hope Cancer Center [17] are testing the combination of busulfan, TBI, and etoposide, with encouraging preliminary results, and investigators from the Fred Hutchinson Cancer Research Center are incorporating targeted radioimmunotherapy into the transplantation regimen [18,19]. Of note, older age in patients with AML is often associated with adverse prognostic factors, such as unfavorable cytogenetics. Thus, they tend to have refractory disease, and intensifying the regimens may not be possible; more novel approaches, such as phase I agents, should be explored.

In conclusion, allogeneic SCT can cure approximately one third of the patients with primary refractory AML. Cytogenetic characteristics before SCT correlate with posttransplantation outcomes and relapse. All patients with AML should be referred for transplantation evaluation at the first sign of treatment failure to optimize transplantation outcome.

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